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ORIGINAL ARTICLES

COMPARATIVE VALUE OF THE METHODS OF TREATING TETANUS.[1]

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This study will not deal with (1) the prophylactic treatment of tetanus, (2) the surgical treatment of the wound or condition underlying the tetanus, (3) the general sedative treatment. The omission of these subjects is not due to any lack of recognition of their importance or necessity, but for the sake of brevity it is assumed that the last two requirements will be carried out so thoroughly as feasible.

My personal experience in the treatment of tetanus is limited to 8 cases; 3 cases died while 5 survived. Of these the first 2 fatal cases did not have the benefit of the more modern or radical methods, whereas the last 6 are characterized by having received antitoxin intraspinally. Of these 6 cases so treated since 1907 only 1 died, a mortality of 17 per cent. The following is a history of the cases, and I add one treated by my colleague, Dr. J. C. Roper, on the First Medical Division of the New York Hospital, which he has kindly allowed me to utilize:

Case I.—Sarah B. Previous operation by me for ovarian cyst. Convalescence normal. Operation at the General Memorial Hospital September 5, 1902, for similar condition. Convalescence normal up to September 16; wound healed by primary union. That day pain in shoulder and back developed, with pain and stiffness in masseters. September 17, 20 c.c. of tetanus antitoxin was administered subcutaneously every six hours. There was general muscular twitching. From September 17 to day of death, September 23, patient kept quiet with morphin. Muscular rigidity general, most pronounced along spine. Masseters relaxed after 40 c.c. of tetanus antitoxin had been given. There is no definite record of the exact amount of antitoxin given or its equivalent in units. Incubation not known. If infection began at time of operation it would be eleven days; if it were due to liberation of tetanus organisms contained in the catgut allowance would have to be made for the disintegration of the catgut. Antemortem temperature, 109.8°. Tetanus developing after an abdominal operation rarely, if ever, recovers.

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[1] Read before the American Surgical Association, Washington, D. C., May 10, 1916.

CASE II.—John E. Policeman. Admitted to St. Luke's Hospital January 28, 1905. Died in twenty-four hours.

Present History. In attempting to stop a runaway horse he was thrown to the ground, cutting the little finger of his right hand. (Exact date of incubation unknown, but very acute.)

Chief Complaint. Irrational, convulsions.

Physical Examination. Head drawn back and neck and back rigid. Jaws fixed. Arms and legs are stiff. On dorsal aspect of terminal phalanx of right little finger there is a lateral wound.

Operation. Amputation of little finger. Exposure of brachial plexus and injection of 20 c.c. of tetanus antitoxin into nerves. Wound left open for future similar injections. Shortly after operation patient had slight convulsive contraction affecting entire body. At 1.45 A.M., January 29, severe convulsion. Patient very cyanotic. 9.45 A.M., dressing removed. 20 c.c. of tetanus antitoxin injected into the axillary nerves. 11 A.M., severe muscular contraction; patient died.

CASE III.—Joseph G., aged forty years. Admitted to Hudson Street Hospital May 28, 1907. Discharged June 23, 1907. One week before admission, while at work, patient caught his right hand in a press, causing a severe compound fracture of the tip of the right thumb and the right index finger. The index finger was amputated at the metacarpal phalangeal joint, the operation being done in the dispensary. Patient returned daily for dressings, and was apparently improving, when on the day of admission he complained of stiff jaw, being unable to open his mouth more than a half inch. On May 29 the right brachial plexus was exposed under a general anesthetic and 60 c.c. of tetanus antitoxin injected into the nerve sheath. On May 31 two 20 c.c. doses of tetanus antitoxin were injected intravenously. Still marked rigidity of muscles of the cheeks, neck, and back. These were repeated on June 1. On June 2 still marked rigidity of back and thighs. Patient had involuntary spasms of the muscles of the thigh, causing him much pain. These spasms involved all muscles of the lower extremities. Patient was not incontinent at any time. Did not suffer with retention. Could move forearm freely, but movements of the right shoulder were less free, giving some discomfort. From June 3 to 11, 20 c.c. of antitoxin was injected intravenously daily (except June 6, 8 and 10). On June 12 there was marked improvement. Muscles of cheek, neck, and back less irritable and spastic. Thighs still rigid on slight palpation. On June 15 condition was much better. There was less rigidity in the thigh and the patient could open his mouth better and could flex the knees and thighs. Discharged cured June 23. Total amount of antitoxin 260 c.c., or 19,500 units (New York City Board of Health). Incubation unknown.

Case IV.—Edward Mc., aged thirty-four years. Admitted to Hudson Street Hospital June 10, 1908. Discharged July 2, 1908. Incubation not known. About one year ago an ulcer broke out on the right leg. It has been healed up twice but recurred. Slept last night in the park. Felt all right when he went to sleep, but when he awoke this morning his legs felt stiff and numb as "if asleep." Sat a while to rest them, and when he started away he fell, and because of stiffness of his legs and thighs was unable to rise. Found by ambulance surgeon doubled up on the curbstone. During the day he has had no pain, but every time he has endeavored to stand his legs would cramp and the muscles become tense and hard, also the pectoral muscles would cramp from time to time. He thinks that for the past two days he has had difficulty in swallowing. He had nothing to eat all day today, so did not notice anything the matter with his jaws. On June 11, 1500 units of tetanus antitoxin were injected intravenously. Two later doses of 1500 units each. He received daily thereafter until June 17, 1500 units of antitoxin (Board of Health) subcutaneously and 1500 units intravenously. June 18 and 19 the 3000 units were all given subcutaneously. On June 23 the patient was considered cured and he was discharged June 30 in excellent condition. Total amount of antitoxin 34,500 units; 15,000 units intravenously, 19,500 subcutaneously.

Case V.—John F., aged four years. Admitted to St. Luke's Hospital April 1, 1909. Died April 11, 1909. Run over by a street car and was dragged for some distance, the wheels passing over his left foot. Foot severely lacerated; all the phalanges were crushed and traumatically amputated. Both femora were fractured. On April 6, amputation at the lower third of the leg. April 8, 11.45 A.M., signs of tetanus first appeared. 7 P.M., 600 units of tetanus antitoxin were given intravenously. At 9.15 P.M., under chloroform anesthesia, the anterior crural nerve of the left thigh and its three branches were exposed. The nerve sheath was injected with 150 units of tetanus antitoxin. Sciatic nerve on left side exposed and sheath injected with 150 units. April 9, 1500 units of antitoxin were injected into the abdominal wall. Patient unable to open jaws at all. At midnight ♏vii tetanus antitoxin were given in the anterior crural and sciatic nerves. April 10, 1500 units were injected into the abdominal wall (9.30 A.M.); 12 M., ♏vii tetanus antitoxin were injected into the sheath of the anterior crural nerve on the left side and the sheath of the sciatic nerve; 8.30 P.M., 500 units of tetanus antitoxin injected intravenously; 10.45 P.M., 800 units of tetanus antitoxin were injected into the abdominal wall. Patient died April 11 at 7 A.M. Incubation seven days.

CASE VI.—Thomas B., aged thirty-two years. Admitted to the New York Hospital April 1, 1914. Discharged April 30, 1914. Incubation ten days. On day of admission the patient was caught between a train and the foundation wall at the Pennsylvania Station. Extensive laceration and traumatic amputation of all the toes of the right foot. Two days after admission the toes were amputated. Ten days after admission (eight days after operation) first signs of tetanus—stiffness of jaws. Antitoxin treatment begun at once. It consisted of the following:

	Intraneural units.	Intravenous units.	Intramuscular units.	Intraspinal units.	Subcutaneous units.
April 11	1,500	3,500			
	3,000				
April 12	5,000	3,000			
	3,000	10,000	7000		
April 13	....	9,000	....	8000	3000
April 15	....	7,500			
April 17	....	5,000			
	12,500	38,000	7000	8000	3000

Total, 68,500 units.

Also three doses, 1 c.c. (1 per cent.) of carbolic acid.

Last injection of antitoxin given the sixteenth day after admission. Discharged twenty-nine days after admission, cured.

This was a very severe case with opisthotonos, general convulsions, and coma. In the single intraspinal injection, done April 13, 4 ounces of clear fluid were drawn off under marked increased pressure, followed by the injection of 8000 units into the spinal canal. It was followed by a temperature of 105.2° and temporary aggravation of symptoms, but on April 16 his condition improved markedly. On April 20 all symptoms disappeared, his mouth could be opened normally, and he was discharged in excellent condition April 30.

CASE VII.—Glen T., aged ten years. Admitted to the New York Hospital October 9, 1914. Incubation seven days. Seven days ago he ran a nail into the sole of his foot. On the day of admission the first signs of tetanus appeared. The family physician administered one injection of tetanus antitoxin and sent the boy to the hospital. On admission the jaws were tightly locked; temperature 100°. Two hours later 3000 units of antitoxin (Board of Health) were administered intraspinally and 1500 about the wound. Next day the temperature was 106° and the patient had frequent general convulsions. Condition continued critical, and on October 13, under chloroform anesthesia, 5000 units were injected intraspinally. It was noted that the fluid was milky in appearance. Temperature 104° next day, but on October 15 all symptoms abated and he improved rapidly. On October 19 he could open his mouth nearly normally, and was discharged October 24 rapidly gaining in strength, with all tetanic symptoms and signs entirely gone.

Summary of Antitoxin Treatment.

	Intraspinal units.	Intravenous units.	Subcutaneous units.
October 9	3000	10,000	1500
October 10	....	9,000	
October 13	5000		
	8000	19,000	1500

Total, 28,500 units.

Case VIII.—Henry S., aged twenty-eight years. Admitted to the New York Hospital September 5, 1915. Incubation seven days. History of having fallen from a tree the day before, a distance of fifteen feet, landing with the right forearm outstretched. Examination shows compound fracture of forearm with low grade of infection. First signs of tetanus appeared September 11, six days after admission. Patient could not open his mouth. Under a general anesthetic 5000 units of tetanus antitoxin were injected intraspinally, 10,000 units intravenously, and 5000 units subcutaneously. Subsequent intraspinal injections done under local anesthesia. On September 27 condition began to improve. On October 11 he could open his jaws about one-half their normal capacity. On October 18 all evidence of tetanus had disappeared, and he was discharged October 31 with tetanus cured.

Summary of Antitoxin Treatment.

	Intraspinal units.	Intravenous units.	Subcutaneous units.	
Sept. 11	5,000	10,000	5,000	5000 in vicinity
Sept. 12	4,000	10,000 12,000	5,000	of ulnar nerve.
Sept. 13	5,000	10,000		
Sept. 14	5,000	15,000		
Sept. 15	5,000	17,000		
Sept. 16	5,000	10,000		
Sept. 18	....	10,000	15,000	
Sept. 19	....	.....	1,000	
Sept. 20	....	15,000		
	29,000	109,000	26,000	

Total, 169,000 units.

This was a very severe case, complicated by a very extensive and severe compound fracture.

CASE IX.—Samuel N., aged twenty-four years. Admitted to the New York Hospital, service of Dr. J. C. Roper, September 5, 1915. Discharged September 25, 1915. Incubation three days (?). Patient was cut in palm of hand September 2 (three days before admission). Wound was dirty, but was well cleaned out and painted with iodin. That evening pain between the shoulders came on and the first signs of "lock-jaw." Since then these symptoms have grown steadily worse. On admission the neck is very stiff, both for lateral and anteroposterior movements. Cannot open the teeth more than 1.5 cm. Is unable to swallow. No history of convulsions. Superficial wound about 1.5 cm. long on the palm of the left hand. Not tender on pressure—not inflamed. On day of admission, under local anesthesia, lumbar puncture was done with injection of 3000 units of tetanus antitoxin intraspinally. This was repeated three times—(4500, 4500, and 5000 units). After the last injection, on September 8, he improved steadily. On September 12 the patient was up in a chair, and was discharged September 25, in good condition.

SUMMARY OF ANTITOXIN TREATMENT.

	Intraspinal units.	Intravenous units.
Sept. 5	1,500	10,500
Sept. 6	4,500	10,500
Sept. 7	4,500	10,000
Sept. 8	5,000	9,000
Sept. 9	....	15,000
Sept. 10	....	15,000
Sept. 11	....	15,000
	15,500	85,000

Total, 100,500 units.

Spinal fluid culture:
Sept. 5. Sterile five days.
Sept. 6. Sterile four days.
Sept. 7. Two spinal fluid cultures in agar tubes—both contaminated—Staphylococcus albus.

Although my personal experience is limited, I feel that the main reliance of the treatment of a well-marked case of tetanus should be along the lines employed in these last 4 cases, a combination of intraspinal and intravenous, also at the onset, local injection at the site of infection. With the more radical localization of the antitoxin in the nerve centers by the intraspinal method it seems to me unnecessary to make intraneural injections, and particularly if that procedure requires the administration of a general anesthetic and the time necessary for the careful dissection and exposure of the nerves. While the line of treatment outlined above impresses me most favorably, I realize that there are many divergent opinions, and that it is dangerous to draw conclusions from a limited number of cases even though successful. Statistics regarding the favorable results of any kind of treatment for tetanus are open to all the objections attending statistical information. Undoubtedly the cases of tetanus vary very greatly in their severity. Certain cases might really be classified as hyperacute, and it is doubtful if they will ever give favorable results. Others are distinctly of a very mild or chronic type; sometimes of a recurring type. Generally speaking the period of incubation has a general prognostic import; that is, short incubations seem to give rise to consistently severe symptoms, and *vice versa*, but even with this standard as a basis there are a good many sources of error. An important factor is the severity of the underlying wound or injury and the kind of treatment it receives or can receive. For that reason it is difficult or impossible to make any very satisfactory deductions from the experience obtained in the treatment of tetanus by wounds inflicted in war where the element of infection, surgical treatment, and after care play such a vital part. Therefore it seems that more logical deductions can be obtained from observation of cases of tetanus occurring in civil life. The nature of the remedial agents employed may also vary greatly, particularly as regards the strength of the antitoxin. In this country we shall soon have a pretty definite standard, thanks to the extraordinarily efficient and intelligent work of standardization of such agents by the United States Public Health Service and the increasing facilities for obtaining reliable preparations of antitoxin manufactured by State and municipal authorities in conformity with such standards. It has been shown by a number of observers that many preparations of tetanus antitoxin, especially those made abroad, vary tremendously in their strength and composition, and it would be manifestly impossible for a foreigner to utilize the recommendations contained in this paper without comparing the relative strength of the preparations at his disposal.

THE STANDARD OF MORTALITY. Broadly speaking, we ought to be able to establish two periods for our observations; one before the introduction of any so-called specific treatment, the treatment then being limited to the administration of a sedative whose necessity has always been recognized. We have two important statistics covering that era in the mortality of tetanus; during the Civil War 89.3 per cent. and the Franco-Prussian War 90 per cent. These observations, however, fall within the preantiseptic era. The paper of Ashhurst and John[2] (which contains the most satisfactory and intelligent exposition of the subject up to date) gives a series of 435 cases from 1897 to 1911, contributed by thirteen authors, with a mortality of 66 per cent. Another and most important factor is the promptness with which treatment is begun. It is my belief, though quite impossible to state it statistically, that this element is a most important factor, and I recommend breaking all speed laws to carry it out. We should be fully as prompt as in the treatment of an acute perforation of the gastro-intestinal tract. In a small proportion of cases it may be possible to recognize preliminary manifestations before the disease asserts itself in its classical manifestations. Localized cramps or twitching of the extremities may be recognized if anticipated. In 20 per cent. of cases it is stated that trismus is not the first symptom. The recognition of tetanus bacilli in the wound and the possible development of diagnostic serum reactions should be of assistance.

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[2] AM. JOUR. MED. SCI., June, 1913.

CHOICE OF TREATMENT. The number of remedial measures suggested is almost infinite. Three stand out today from all others, namely, antitoxin, magnesium sulphate, and carbolic acid. Only these three will receive here any serious consideration.

It may be interesting to study the various forms of treatment now being used in the European war, although a study of results will have to be deferred till accurate reports can be collected.

TREATMENT OF TETANUS IN THE PRESENT EUROPEAN WAR. One obtains the impression that at present (1916) the amount of tetanus is not very great, notwithstanding that the trench fighting and the severe cold with its consequent frost-bites would favor its development. There appears to have been a good deal of tetanus in the early conflict, but the increasing prophylactic treatment with antitoxin now seems to be keeping it in check.

One finds as much diversity in the treatment of tetanus in military life as in civil, and the customs seem to vary largely in the various countries.

TREATMENT OF TETANUS IN ENGLAND. The most satisfactory exposition of the treatment is contained in a little booklet *Memorandum on the Treatment of Injuries in War, Based on Experience of the Present Campaign*, July, 1915, published by the Royal Army Medical Corps. It is given in full, as it seems to be the best single comment on the methods available. It will be noted that the administration of tetanus antitoxin, and particularly the intraspinal method, is the method of choice:

"TETANUS. The heavily manured soil of the districts in which fighting has occurred frequently contains the spores of tetanus bacilli; these, in many wounds, are driven deep into the tissues and may find there the anaërobic conditions suitable for their development. Should the bacilli establish themselves in such a wound they give rise to toxins which have a great affinity for nervous tissues and produce the well-known symptoms of the disease.

"PREVENTION. A. *General Measures*. The steps advocated in other parts of this pamphlet for the cleaning, dressing and drainage of freshly received wounds, as well as for their appropriate surgical treatment, with a view to minimizing the risks of sepsis, are those which, if fully carried out, will also minimize the risk of tetanus. They need not, therefore, be further described here.

"B. *Special Measures.* These resolve themselves into the prophylactic use of tetanus antitoxin, a proceeding of well-established value.

"*Prophylactic Use of Tetanus Antitoxin.* Since in the first two months of the war more cases of tetanus occurred than had been anticipated, either by ourselves or our Allies, it was decided to direct that a preventive dose of serum should be given to every wounded man in place of leaving this, as had been done at first, to the discretion of the medical officer. The results have been excellent, and, in the last six months, there have only been 36 cases of the disease among those who received a preventive dose of serum within twenty-four hours of being wounded. That this is not due to the possible absence of the cause of infection from the soil is clear from the following facts: (1) Bacteriological examination of the wounds has often proved the presence of tetanus bacilli, although no tetanic symptoms have followed. (2) Many instances of slight trismus, or of localized tetanic spasms of a muscle or a group of muscles, have been reported, without the subsequent development of generalized tetanus. (3) Thirty-four cases of severe tetanus have been reported in this period among the very small fraction of wounded men who, for one reason or another, had not received a preventive dose of the serum within twenty-four hours. (4) A considerable number of wounded horses continue to develop the disease.

"The general use of preventive inoculation of the serum has also had an effect on the severity of the symptoms if, in spite of the preventive dose, the disease should subsequently develop. For example, of the 34 cases mentioned above, which did not have a preventive dose within twenty-four hours, 32 died, a case mortality of 94.1 per cent.; whereas of the 36 cases which occurred among the enormously larger class of wounded who *had* received a preventive dose, 28 died, a case mortality of 77.7 per cent.

"The preventive dose of 500 units should be given subcutaneously at a distance from the wound at the earliest possible moment, and the fact of inoculation, as well as the size of the dose, should invariably be recorded on the 'tally.' In severe wounds medical officers not infrequently give 1500 units; there is no objection to this, but at the same time there is no evidence that the smaller dose is insufficient if given promptly.

"It should be remembered that injuries other than those caused by bullets or shells may also become infected; several fatal cases have followed trivial injuries, for which the soldier did not report sick at the time, and others have followed on the gangrene due to frost-bite. It would be wise to give a preventive dose in all instances in which the danger of infection of a wound with contaminated soil may be presumed to exist.

"Several different preparations of tetanus antitoxin are in use. These have all been recently tested, and in each case they were found to contain at least the number of units claimed.

" (The question of Anaphylaxis is dealt with below.)

"*Influence of the Duration of the Incubation Period on the Severity of the Attack.* The general experience has been, as was to be expected, that the shorter the interval between the receipt of the wound and the appearance of the symptoms the smaller the chance of recovery. At the same time, cases have recovered in which the symptoms appeared six days after the wound, and cases have proved fatal where nineteen days had elapsed. The average incubation period of 43 fatal cases was 8.83 days, and that of 26 cases which recovered 11.57 days.

"TREATMENT WHEN THE DISEASE IS ESTABLISHED. A careful study has been made of 179 cases in which certain particulars which had been called for were furnished. Of these 179 cases, 140 have died, a case mortality of 78.2 per cent. Although this figure is disappointingly high, it must not be forgotten that the majority of these cases were also suffering from severe forms of sepsis, and in a considerable number of them the reporting officer stated that the tetanic symptoms had completely subsided under treatment, the patient dying from septicemia, gangrene, secondary hemorrhage, or other causes.

"A. *Local and Surgical Measures.* Steps should be taken to open up and clean the wound, if this has not already been done, and the freest possible drainage should be secured. The local application of strong antiseptics, swabbing with pure carbolic acid, the free use of hydrogen peroxide, and similar measures, have been tried, but appear to have had little influence on the course of the disease. Surgical interference of a grave nature, such as amputation of a limb, has been carried out in a number of instances; but such cases have almost always died, though not necessarily from the severity of the tetanic symptoms.

"B. *General Measures.* The patient should be kept in a perfectly quiet and darkened room, maintained, as far as possible, at an equable temperature. The avoidance of all external stimuli, likely to start a spasm, is to be aimed at, and some have advocated the bandaging of the eyes, the plugging of the ears with wool, the placing of the feet of the bed on rubber disks, etc., with this object in view. It is of great importance to maintain the strength of the patient by means of adequate fluid nourishment, given in small quantities at frequent intervals, and by the rectum if swallowing tends to induce spasm.

"C. *Use of Anesthetics and Sedatives.* As regards the former, chloroform is most commonly used, though ether has been preferred by some, especially when required for a small operation or for the dressing of a painful wound. Their value is well recognized. As sedatives, chloral hydrate, potassium bromide, and morphin are most frequently used for the purpose of controlling spasm, the first named being the most valuable. They are of undoubted value in this direction, but do not appear to modify the course of the disease to any great extent. Too frequent or too large doses may do harm. Chloretone, in doses of 30 to 40 grains in olive oil, given by the rectum, has been well spoken of for the same purpose of controlling spasm.

"D. *Carbolic Acid Method.* This has been given a trial in a considerable number of cases, usually in combination with tetanus antitoxin, but the results have been disappointing. The dosage must be considerable and the treatment must be kept up well into convalescence; in one case a relapse was reported to have followed its abrupt discontinuance. The following strengths of carbolic acid have been recommended:

I. 20 c.c. doses of a 1 per cent. solution.
II. 20 minim doses of a 2 per cent. solution.
III. 2 c.c. doses of a 5 per cent. solution.

"The inoculations are made either subcutaneously or intramuscularly every three or four hours, the interval between the doses being lengthened as the spasms diminish in frequency. In no case has any local trouble been reported, nor has carboluria followed even large and frequently repeated doses.

"E. *Magnesium Sulphate.* Three methods of employing this drug have been advocated: (*a*) The subcutaneous inoculation of doses of 2 c.c. of a 25 per cent. solution. (*b*) The subcutaneous inoculation of large quantities of a more diluted solution, Greely recommending the injection of a 1 to 2 per cent. solution in quantities varying from 1 pint to 1 quart every three hours, according to the severity of the case. (*c*) The intrathecal method. For this Philips advises the inoculation of a 25 per cent. solution, after withdrawing some of the cerebrospinal fluid, 1 c.c. being given for each 25 pounds of body weight, corresponding to 5 or 6 c.c. for a man of average size. The head of the bed should be propped up after the operation. The advocates of this method claim that it gives relief from pain, controls spasm, and ensures sleep. It has been used in this war chiefly by the intrathecal method, but, like carbolic acid, has not proved reliable.

"F. *Tetanus Antitoxin.* This is the only treatment as to the employment of which there has been anything like general agreement. It has been used in one form or another in almost every case, and when cure has resulted it has commonly been given the credit. Whatever method be employed it is clear that three general principles must be observed to obtain the best results: (1) It must be employed at the earliest moment possible; a dose of 1000 to 1500 units given at a time when there is little more than a fear that tetanus may develop, may influence the course of the disease favorably. (2) It must be given in large doses, and these should be frequently repeated until the symptoms show definite signs of amelioration. (3) It must be kept up, although in smaller and less frequent doses, well into convalescence, in order to obviate the tendency to relapse.

"The most favorable results appear to have been obtained by the employment, in the first instance, of the intrathecal combined with the intravenous methods, the subcutaneous method being used to reinforce the others in the succeeding days or to replace them as the symptoms diminish in intensity.

"*Dosage.* An initial intrathecal dose of 3000 units followed by the intravenous injection of doses ranging between 5000 and 20,000 units, according to the severity of the symptoms, has been reported in many instances to have had a favorable effect. In severe cases the intrathecal dose of 3000 units may be repeated the next day. The subsequent indications as to dosage depend upon the progress of the case; if this is favorable the above methods may be supplemented or replaced by the subcutaneous one, doses of from 5000 to 10,000 units being given every day or every second day.

"*Anaphylaxis.* Symptoms of this grave condition are well known in animals to follow the administration of a second dose of the same serum when the lapse of time between the two doses exceeds ten or twelve days. There was some reason to fear its occurrence in men who had received a preventive dose of tetanus serum after being wounded, and who, on account of the development of the disease after an interval of twelve days or more, were given therapeutic doses of the same serum. Again, a large number of men who have returned to the front after recovery from a wound are again wounded, and the question has been raised as to the possible danger of giving another preventive dose of serum after an interval of some weeks or months. It is, however, well known that man is much less sensitive to anaphylaxis than the guinea-pig and the rabbit, and this has been fully borne out by the experience of the war. In spite of close inquiries on the subject no certain instance of true anaphylaxis has been recorded. The few cases which have been mentioned in reports have, on investigation, turned out to be instances of serum sickness and to have had no grave results. It does not, therefore, appear to be justifiable to withhold the serum in the case of a man wounded for the second time; at all events, it appears better to run the small and chiefly theoretical danger of anaphylaxis than the very grave one of tetanus.

"In cases in which there is reason to fear the occurrence of anaphylactic shock, various procedures have been recommended to lessen the danger. The majority of these are "fractional" methods of administering the serum, a preliminary inoculation of 2 or 3 drops of the serum being given, in dilution, followed in five minutes by a dose of 0.5 c.c. If no untoward symptoms result it is said that the full dose may safely be inoculated ten minutes later. A similar fractional method has been advised if the intrathecal methods are selected, but there has been no opportunity of judging of their value. Administration of the serum under chloroform anesthesia is also said to lessen the danger. If symptoms of shock should develop in spite of these precautions, adrenalin has been stated to be useful, given intravenously in high dilution if the symptoms are urgent, hypodermically in less urgent condition in doses of a few minims of a 1 to 1000 solution."

TREATMENT OF TETANUS IN ITALY. Dr. Carlo Savini, of New York City, who has recently returned from the Italian war zone, writes under date of October 22, 1915, as follows:

"The consensus of opinion in Italy seems to be very favorable to the Bacelli treatment of tetanus. It is claimed to give only 17 per cent. mortality, while the symptomatic (or expectant) and the antitetanic serum treatment give from 50 per cent. to 78 per cent. mortality.

In the war zone the prophylactic injection of antitetanic serum is compulsory for all the wounded, and I was told that very few cases of tetanus are found.

The treatment of tetanus is left to the judgment of each doctor, and it is not possible now to state how often the Bacelli treatment is being used and what the results are.

In conclusion, in Italy everybody agrees in the prophylactic value of the serum. In the therapy of tetanus the treatment of Bacelli seems to be the most favored; next is the treatment with injection of magnesium sulphate solution, and last the treatment with antitetanic serum."

Professor R. Bastianelli writes under date of December 12, 1915:

"I am not able to answer satisfactorily your question about the treatment of tetanus in Italy. The present war has given ample occasion to collect experience on that argument, but the results are not yet tabulated. Prior to the war, Bacelli's method was used extensively by us and the reports have been satisfactory. It is possible, however, that many unfavorable cases have not been reported. The antitoxic method, either with Tizzoni's antitoxin or with Behring's serum, has been employed extensively, and so far as I know with rather good results in cases with late onset and slow course, while in the so-called acute cases the results have been very poor and in my experience constantly bad. I have used the serum intravenously and intraspinally at the same time, giving also large doses of chloral and intramuscular injections of magnesium sulphate."

TREATMENT OF TETANUS IN FRANCE. In France there is also no distinct line of treatment. October 11, 1915, Dr. Charles Walther writes me:

"I find it difficult to give you exact information, as I doubt if there is a single method of treatment of tetanus which is generally accepted. In addition to the classical treatment by heat, dark room, administration of chloral, I find there is a tendency to employ more and more antitetanic serum in large doses, 40 to 50 to 60 cm. daily subcutaneously or intravenously. Intraspinal injections in considerable amounts, between 40 and 60 c.c., every second day, with head and trunk lowered, seem to have given good results. Personally, I have had a certain number of successes in the intravenous and subcutaneous injections of antitoxin in large amounts, particularly of peripharyngeal injections in the subhyoid region at the base of the tongue.

"I believe I was the first, fourteen years ago, to make intraspinal injection of antitetanus serum in a case at the La Pitié Hospital. I have personally no experience in the use of magnesium sulphate or carbolic acid."

TREATMENT OF TETANUS IN BELGIUM. The treatment most favored by Dr. Depage when I saw him in February, 1915, was the antitetanus toxin, but I do not think he ever used it intraspinally.

I have not heard directly from the other fronts and can only surmise as to the methods employed. Stolbnyak states, in the *Russkiy Vrach*, Petrograd, summarized in the *Journal of the American Medical Association*, January 15, 1916, page 232:

"The best symptomatic results were obtained with chloral hydrate, from 1 to 7 gms. daily given by the mouth or rectum. For spasmodic contracture of the intestines and bladder hypodermic injection of from 0.5 to 1 gm. of a pituitary extract gave good results. Warm baths at 100° F. also proved effectual in symptomatic treatment. No benefit could be detected from treatment with antitetanus serum, intravenous or intraspinal; from 3 per cent. phenol solution; suspensions of pigs' brains; calcium lactate three times daily in doses of 30 drops of a 10 per cent. solution, or from magnesium sulphate in hypodermic injections of from 2 to 14 c.c. of a 25 per cent. solution, or by intraspinal injection of 15 c.c. of a 10 per cent. solution."

In Germany the treatment seems to be most varied, and includes a number of methods which would seem to have little but their novelty to recommend them. Violet light, salvarsan, ascitic fluid from cured patients, emulsion of pigs' brains, intravenous injections of ether, etc.

The method which seems to be most in favor is the magnesium sulphate treatment, particularly when injected into the spinal canal. Kocher's favorable report on its use seems to be responsible for its popularity.

COMPARATIVE CLAIMS OF ANTITOXIN TREATMENT, MAGNESIUM SULPHATE AND CARBOLIC ACID. As has been stated before, it seems quite impossible at present to establish anything like a statistical investigation with any hope of accurate results. Only if very large groups treated under similar conditions should show marked discrepancy in results would it be safe to draw any deductions.

THE ANTITOXIN TREATMENT. The antitoxin treatment may be divided into (*a*) subcutaneous administration, (*b*) intravenous, (*c*) intraspinal, (*d*) intraneural, (*e*) intracerebral. The last method we can dismiss, as it is no longer employed, and gave very bad results; the other methods promise better.

(*a*) The subcutaneous method, it is believed, lacks efficiency and should be used only as an adjuvant to the other methods.

(*b*) The intravenous administration is a distinct advance as regards efficiency and rapidity of results. My belief is, however, that it should be considered as an accessory rather than the main line of treatment.

(*c*) The intraspinal method appeals to me as complying most with the indications, namely, locating the antitoxin most directly to the lesion itself. Ashhurst and John have presented conclusively the evidence that the toxin of tetanus reaches the spinal cord by the peripheral nerves. They state that "the nearer the toxin gets to the spinal cord the more impregnably intrenched does it become in the nerve tissue."

It is not easy to determine who was the first responsible for the idea of injecting the antitoxin intraspinally. I find no mention of it prior to Schultze's article in the *Grenzgebiete der Medizin und Chirurgie.*

Personally, I have been much impressed with the evidence furnished by the experimental work and clinical results of Dr. W. H. Park and Dr. M. Nicoll, Jr., from the laboratory of the New York City Board of Health. I may state that in all my successful cases here reported the treatment has been conducted entirely on the lines laid down by these gentlemen and with their advice and coöperation. In the *Journal of the American Medical Association,* June 12, 1915, Nicoll reports 20 cases treated with the chief reliance on intraspinal injections, with 4 deaths. These cases represent an average severity, were under the care of different physicians and under varying conditions.

They recommend (1) from 3000 to 5000 units in the lumbar region of the spinal canal, preferably under an anesthetic,[3] the volume of fluid injected being brought up to 10 or 15 c.c. by the addition of sterile or normal saline, the exact amount being regulated to the age of the patient and the amount of spinal fluid withdrawn; (2) 10,000 intravenously at the same time; (3) repetition of the intraspinal dose in twenty-four hours; (4) subcutaneous dose of 10,000 units three or four days later.

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[3] This recommendation of the author, I think, will be only exceptionally necessary, *e. g.*, in the case of children. It is important to remember this fact as the recommendation to *give* an anesthetic might deter some from utilizing this valuable method.—C. L. G.

The above directions may suffice in a case of ordinary severity, but we believe that many cases will have to receive more antitoxin intraspinally than the two injections recommended and a good deal more intravenously. Case VIII received 6 injections, 29,000 units of antitoxin intraspinally and antitoxin in other forms up to 169,000 units.

I am inclined to think that in the future we shall use greater amounts of antitoxin intraspinally and especially in the initial dose. Dr. Boyd, of Springfield, recently reported a case of a young child in which treatment was begun at the end of a week, the child being then apparently moribund. Under an initial dose of 15,000 units intraspinally the patient made a prompt response and good recovery. I am inclined to think that in future cases of great severity I shall also begin with as large or possibly even larger dose.

In a mild case some question may arise as to whether more than the initial intraspinal dose should be administered. If improvement becomes manifest at once the second intraspinal dose may be well withheld, but the antitoxin intravenously should be administered daily until the improvement is certain. A guide to the necessity for antitoxin treatment may be had in estimating the antitoxic contents of the blood. This procedure, however, requires the coöperation of an expert worker, and is time-consuming and not really necessary. There is probably very little danger in overdoing the dosage so long as active symptoms of tetanus are present. The fluid withdrawn from the spinal canal after the preliminary injection of antitoxin has a milky tinge, but was found in our cases to be quite sterile.

(*d*) If we accept the value of the intraspinal injection of antitoxin there seems to be little call for intraneural injections which some fifteen years ago were extensively employed and apparently with an improvement over the then commonly used methods. Unless better evidence can be furnished of the value of intraneural injections they can be eliminated, for they require the performance of a formal operation under an anesthetic which in the patient's grave condition is inadvisable, besides being a more formidable procedure than the simple injection intraspinally. If we accept the doctrine that the intraneural injection is superfluous we can also apply this dictum to the amputation of an extremity.

MAGNESIUM SULPHATE. This treatment was originated in the United States by Meltzer and Auer. In the *Journal of the American Medical Association,* March 25, 1916, Meltzer writes of the "Inhibitory Properties of Magnesium Sulphate and their Therapeutic Application in Tetanus." He says:

"The action may appear to some as merely a symptomatic one; it relieves the convulsion. But even if this would be indeed its only favorable effect, it would be of inestimable value, since the suffering in tetanus and the fatal outcome of this horrible disease is nearly exclusively due to the consequences of the tetanic symptoms. And I may assert that no other remedy is capable of relieving the furious symptoms to such a satisfactory degree as do the injections of magnesium sulphate."

Magnesium sulphate can be administered intraspinally, subcutaneously, intravenously, intramuscularly plus ether inhalation. Meltzer summarizes the treatment as follows:

"The best general plan for treatment of tetanus would seem to be as follows:

"In each and every case of tetanus, 1.2 c.c. of a 25 per cent. solution of magnesium sulphate should be given by subcutaneous injection three or four times a day throughout the entire disease.

"When the disease is complicated by severe tetanic attacks, 1 c.c. of a 25 per cent. solution for every 10 kg. (20 pounds) body weight (in adults) should be given by the intraspinal method.

"When the disease is attended by immediately dangerous tetanic complications, from 2 to 3 c.c. per minute of a 6 per cent. solution of magnesium salts should be given then by an intravenous injection until dangerous symptoms subside or the respiration becomes shallow or too slow.

"When the respiration seems to become impaired in consequence of the administration of magnesium salt by the intravenous, intramuscular, or subcutaneous methods, calcium chloride should be injected in the manner described above.

"It is advisable to have at hand an apparatus of intrapharyngeal insufflation ready for use whenever the respiration becomes slow or shallow.

"Finally the simultaneous treatment by antitetanic serum should not be neglected."

No statistics are given in support of the success of this method of treatment. Reference is made to a favorable report by Kocher.

This treatment was employed at the time of its development in New York City; but the general impression is that it has too many dangers and drawbacks *per se,* particularly in paralyzing the respiration. Its intraspinal administration undoubtedly checks the convulsions more speedily than any other method. I should prefer however, to substitute for it the inhalation of a general anesthetic to a very slight degree as used to be done fifty years ago.

The method was employed quite a little following Meltzer and Auer's original description. Of late there seems to have been little attempt to use it in America, but in the present war it seems to stand out as prominently as any one method in Germany and to some extent in other countries.

Cloetta[4] warns against the use of magnesium sulphate and notes its resemblance to the action of curare which was used in tetanus fifty years ago.

CARBOLIC ACID TREATMENT. This treatment was initiated by Bacelli, according to Ashhurst and John, in 1888. The mortality claimed for it is the lowest of all, 17 per cent. It seems remarkable that it has not come into more general use especially in America. It is administered, according to Ashhurst and John, 1 c.c., 1 per cent. solution, every few hours, perferably into the muscles along the spine, until 80 or 100 centigrams are given in twenty-four hours.

Sainton[5] reports 22 cases of tetanus treated in the French Army Hospitals by the Bacelli method, with 16 deaths. This is not a very favorable showing for the method, but it must be remembered the difficulties of estimating the results of subjects wounded and treated under war conditions.

SUMMARY OF PROPOSED CHOICE OF TREATMENT. As I have stated before, it is presumed that the wound treatment will be that suitable to the injury and particularly to the most efficient form of drainage and liberation of sloughs, removal of foreign bodies, etc., that may harbor tetanus germs or favor their development. I doubt if today we are justified in performing an amputation for the relief of tetanic manifestations as in the intraspinal administration we have gone a step further in efficiency. Likewise, I will omit the questions of nursing and the use of sedatives. One sedative, however, should be alluded to as it has been thought to have curative qualities *per se,* namely the chloretone treatment advocated by Hutchings.[6]

I should also be inclined to make a trial of atropin as a method of controlling spasm, as this drug has lately impressed me greatly in the treatment of spasmodic contraction of the pylorus.

Antitoxin treatment should be begun immediately on suspicion of tetanus developing rather than waiting for the classical symptoms. If this principle is firmly established, I believe we shall have done much to lessen the dangers of the disease. Antitoxin should be given at once, first into the wound or region of the wound, say 1500 units, intraspinally, without an anesthetic, unless the treatment of the wound calls for the administration of a general anesthetic, 5000 to 20,000 units. In the course of the first twenty-four hours, in addition to the above, 10,000 to 20,000 units should be administered intravenously in divided doses, say two or three. Antitoxin intravenously from 5000 to 15,000 units should be given next day no matter whether the symptoms remit or increase. On the third day if, notwithstanding the treatment, the patient's symptoms continue very severe or appear worse the intraspinal

[4] Correnspondenz-Blatt f. schweizer Aerzte, 1915, No. 3.

[5] Journal de Chirurgie, September, 1915.

[6] Annals of Surgery, vol. l.

treatment should be repeated. The intraspinal, of course, gives temporary increase of symptoms and steep elevation of temperature but this fact need not of itself cause alarm. If after this treatment the patient holds his own or improves the intraspinal need not be repeated but the daily injection of antitoxin intravenously should be given until obvious remission or cure results.

The severity of the cases will, of course, vary and the resulting treatment will depend on this factor. Attention is called to Case VIII, who received a total of 169,000 units, which included 29,000 units given intraspinally in six sessions, in this case, daily, although I doubt if this frequency is often indicated.

The series of cases I have reported is, of course, small, and I am fully aware of the dangers of deducing results from such small material. On the other hand, I have the impression, though I find it hard to put into words, that, although many of these cases were of the severest type and very ill, we had, particularly in the intraspinal method, complete control of the situation. With this feeling of confidence, therefore, I should hesitate to offer any other method of treatment until there is better evidence of the superiority of these other methods.

THE PATHOLOGIC CHANGES IN THE SYMPATHETIC SYSTEM IN GOITER.*

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The amount and character of the pathologic changes in the sympathetic ganglia removed at operation or at autopsy from patients with exophthalmic goiter have been studied by other observers, meagerly and rarely by modern methods. I have reviewed elsewhere[1] the literature of previous reports. So far as the findings have been positive, they have shown that in exophthalmic goiter the cells of the sympathetic ganglia exhibit various stages of degeneration. The paucity and incompleteness of the reported observations, however, together with Cannon's[2] recent experimental production of some of the symptoms of exophthalmic goiter in cats by constant stimulation of the thyroid through the sympathetic system, have warranted a more careful study of the material accumulating in the Mayo Clinic.

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* Read before the Association of American Physicians, Washington, D. C., May 10, 1916.